LUNG BIOAVAILABILITY OF GENERIC AND INNOVATOR SALBUTAMOL MDIs

The statement by Clark et al (March 1996; 51:325-6) that “the coefficient of variation for urinary salbutamol was approximately double that for plasma salbutamol” cannot be made with confidence until the authors have validated the protocol they are using. Hindley and Chrystyn suggest that the relative bioavailability of salbutamol to the lung could be used to compare two inhaled products/innovation methods by measuring the amount of salbutamol excreted in the urine in the first 30 minutes after inhalation. Their method was to start at time zero, inhale four consecutive doses (with one minute between each dose), and then provide a urine sample at time t = 30 minutes. The protocol used by Clark et al is 12 sequential inhalations over six minutes and then a urine sample is collected for the measurement of salbutamol excretion 30 minutes after completion of the 12 inhalations. Thus, urine is collected over the first 36 minutes compared with 30 minutes for the method of Hindley and Chrystyn. This the authors confirmed during a poster discussion session at the British Thoracic Society’s winter meeting in December 1995. We have recently been involved with further studies to validate our method so that we can extend our work to the use of nebulisers. At present we have data on five healthy volunteers (three men and two women) who inhaled 100 μg salbutamol solutions at t = 0, 2, 4, 6, and 8 minutes and provided urine samples at 0, 30, 40, and 60 minutes after swallowing the last dose. The mean (SD) rate of salbutamol urinary elimination from t = 0-30, 30-40, and 40-60 minutes was 0.08 (0.11), 0.72 (0.76), and 0.99 (0.38) μg/hour, respectively (linear file). Similar results follow the inhalation of five sequential 100 μg salbutamol inhalations at t = 0, 2, 4, 6, and 8 minutes (that is, each separated by two minutes) (579), 24-16 μg/hour, and 17-60 (6-69) μg/hour, respectively. Thus, interference from the salbutamol delivered to the body by the oral route would be present in the urine samples collected between 30 and 40 minutes after the first inhaled dose. This suggests that the urine samples collected by Clark et al over the first 36 minutes after the start of the first inhalation would include salbutamol absorbed by the oral route. The presence of drug from oral absorption could account for some of the greater variability of their results compared with the reported plasma salbutamol concentrations.

Clark et al claim that the maximum plasma concentration, Cmax, after inhalation may be used as a direct measure of absolute drug bioavailability. However, the measurement of Cmax is an indirect method of bioavailability since it measures salbutamol concentrations in plasma rather than amounts in the lung. Furthermore, the authors do not present supporting data following oral administration to the ten healthy men they studied. The absence of intravenous data or direct intra- instillation into the lungs with their method means that it compares relative lung bioavailability, not absolute.

Finally, we question whether the dosing schedule used by Clark et al would be representative of normal inhaler usage. Although our initial studies have used four inhaled doses, we have now validated our method for one dose (although most of our work is now concentrating on two doses). In the absence of in vivo studies to show that there is no difference in pulmonary deposition and oral ingestion between a few doses and 12 sequential inhalations, the conclusion of Clark et al that the two generic MDIs were similar to the innovator can only be applied if 12 consecutive doses are inhaled by men.

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BOOK NOTICE


This book represents a successful attempt to incorporate in a practical way the huge amount of information published regarding HIV and AIDS since the first edition in 1990. If anything, the term "pocket book" may underestimate the quantity of information which is concisely expressed on every aspect of HIV disease.

There are 18 chapters each by different authors with practical experience in their topic, although the editors have maintained the simplicity of the text of the first edition. This is an update of the authors and providing an overview of current literature. The chapter on therapeutic guidelines comprehensively presents treatment regimens for the major opportunistic infections, including drug side effects and drug interactions. Chapters on HIV in pregnancy, paediatrics, and in relation to blood products and intravenous drug misuse provide updated information of great use to counselling patients. Moreover, there is a chapter providing practical guidelines for counselling HIV patients in general. Especially useful and thought-provoking is the chapter on aspects of palliative and terminal care.

The book has an index and each chapter is referenced. There is a limited number of black and white illustrations.

This excellent book is particularly recommended to medical students, junior hospital doctors including MRCGP students, and general practitioners in high prevalence areas. Chest physicians will find this book useful not only for information on the respiratory manifestations, but also on the diseases of other organ systems likely to coexist in their patients infected with HIV. – DF

NOTICE

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A three-day intensive course on Experimental and Clinical Aspects of Asthma will be held in Ghent, Belgium on 19–21 November 1996. For further information please contact the Department of Respiratory Diseases, University Hospital, De Pintelaan 185, B 9000 Ghent, Belgium. Phone: 32 9 2402011. Fax 32 9 2402341.